Tufts University | School of Engineering

Department of Civil and Environmental Engineering

November 5, 2019

US Environmental Protection Agency
1200 Pennsylvania Avenue NW
Washington, DC 20460

Docket Numbers: EPA-HQ-OAR-2015-0072; EPA-HQ-ORD-2014-0859

Comments of Helen Suh, Justin Manjourides, Ki-Do Eum, Vivian Pun

Regarding the proper interpretation of major findings from our work in Pun et al. (2017) and Eum et al. (2018)

We are writing to comment on issues raised in the public comment by Mr. Stewart E. Holm, Chief Scientist for the American Forest & Paper Association, during the Clean Air Scientific Advisory Committee (CASAC) public comment session on the draft EPA Policy Assessment for Fine Particulate Matter ($PM_{2.5}$) on October 22, 2019, and in individual written comments from Dr. Tony Cox on the Policy Assessment dated October 21, 2019. In discussing the findings from our Pun et al. (2017) [1], Mr. Holm makes factually incorrect statements regarding results from our study and both Mr. Holm and Dr. Cox draw inaccurate conclusions regarding our study findings and their policy relevance.

Here, we discuss the findings from our 2017 paper as they relate to problems with Mr. Holm's and Dr. Cox's description and interpretations. In addition, we address issues of temporal confounding raised by Mr. Holm and Dr. Cox by discussing relevant findings from Eum et al. (2018) [2], which is a companion paper to Pun et al. (2017). In Eum et al. (2018), we examined the association of $PM_{2.5}$ and mortality while controlling for long-term time trends in $PM_{2.5}$ using the Medicare cohort, the same cohort used in the Pun et al. (2017) study. We first summarize findings from Pun et al. (2017) and then discuss our findings in relation to arguments raised by Holm and Dr. Cox.

Summary of Pun et al. (2017)

We found clear and consistent associations of 12-month moving average $PM_{2.5}$ exposures and increased mortality from cardiovascular (CVD) disease, cancer, and for the first time, respiratory disease in a US population of Medicare beneficiaries. We showed significant increased $PM_{2.5}$-associated mortality risks not only for the major causes of death but also for specific causes of death, including ischemic heart disease, cerebrovascular disease, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), pneumonia, and lung cancer. Mortality risks were consistent across the specific causes of death, with risks generally higher for CVD- as compared to respiratory- and cancer-related causes of death. Further, mortality risks were robust to adjustment for area level measures of behavioral risk factors and to stratification by geographic region.

We assessed the potential for unmeasured confounding by comparing the mortality risk ratios for temporal and spatio-temporal components of $PM_{2.5}$, following the methods by Greven et al. [3]. We found the mortality risk ratios between these components to differ, with these differences smaller in models adjusting for behavioral risk factors. These results suggest the presence of unmeasured confounding, which was not completely removed by adjusting for behavioral risk factors alone. The presence of unmeasured confounding after adjustment for behavioral risk factors was expected given that we did not control for several potential confounders that may impact $PM_{2.5}$-mortality associations, such as smoking, socio-economic status (SES), gaseous pollutants, $PM_{2.5}$ components, and long-term time trends in $PM_{2.5}$. These ***potential confounders may impact both temporal and spatio-temporal $PM_{2.5}$***, as, for example, smoking may impact temporal trends in $PM_{2.5}$ through national changes in warning labels on cigarette packages and may also impact spatio-temporal trends in $PM_{2.5}$ through the differential implementation of local laws on cigarette smoking in public spaces. Importantly, while our findings of unequal temporal and spatio-temporal risk ratios indicate unmeasured confounding, they do **NOT** mean that an uncontrolled confounder is the actual culprit nor do they call into question the results from studies of long-term $PM_{2.5}$ and mortality, as evidenced in our discussion below.

Temporal $PM_{2.5}$ findings and implications

Mr. Holm's comments erroneously state that "adjustment for behavioral risk factors produces statistically insignificant risk estimates for temporal $PM_{2.5}$, with values below one for some causes of death". Supplementary Table 4 of Pun et al. shows that temporal $PM_{2.5}$, while attenuated, remained significantly associated with increased mortality for all causes of death (save accidental) after adjustment for behavioral risk factors, with all RRs greater than one.

Mr. Holm uses his incorrect reading of Supplementary Table 4 to argue that there is not a "clear and consistent association" between temporal $PM_{2.5}$ and mortality and as a result, any findings of significant and positive associations between total $PM_{2.5}$ and mortality are suspect due to concerns regarding spatial confounding. This argument is invalid given that (1) it is based on incorrect information, (2) spatial confounding may bias mortality risks both towards and away from the null, and (3) ***spatial confounding alone is unlikely to explain our consistently positive findings, given that we included a fixed effect for location in our models and we controlled for area-level behavioral risk factors.*** While we did find associations with spatio-temporal $PM_{2.5}$ to be largely null, this was expected given that spatio-temporal variation in $PM_{2.5}$ explains just 5.19% of the variance in the monthly $PM_{2.5}$ concentrations at a location [4].

Mortality Risk Ratios in models controlling for temporal confounding

The method of decomposing $PM_{2.5}$ into its temporal and spatio-temporal components developed by Greven et al. [3] is intended to assess whether unmeasured confounding remains. ***This method, however, cannot be used to examine the association of overall $PM_{2.5}$ on mortality controlling for long-term time trends in $PM_{2.5}$.*** This is because the decomposition method explicitly eliminates spatial information, an important component of $PM_{2.5}$ variability. The meaning of each coefficient, absent comparison with the other, thus, is not clear.

For this reason, we examined the impact of long-term time trends in $PM_{2.5}$ on mortality risk estimates explicitly in Eum et al. [2]. We evaluated several potential methods to adjust for long-term time trends in $PM_{2.5}$ and showed that methods based on the residual of the linear regression of $PM_{2.5}$ on time in 4-year intervals successfully remove long-term time trends in $PM_{2.5}$. We used this residual-based method in models estimating the association of 12-month moving average $PM_{2.5}$ exposures and all-cause mortality in US Medicare beneficiaries. ***Even***

after controlling for long-term temporal $PM_{2.5}$ trends, we found a statistically significant 11.7% increase in all-cause mortality among Medicare beneficiaries for a 10 µg/ m^3 increase in $PM_{2.5}$. Our findings were consistent across regions, length of study period, and variations in methods to control for long-term time trends in $PM_{2.5}$. As such, our findings ***provide direct evidence of a significant association between long-term $PM_{2.5}$ exposures and increased mortality that cannot be explained by declining $PM_{2.5}$ levels over time.***

Summary

Together, findings from Pun et al. (2017) and Eum et al. (2018) provide compelling evidence of a clear and consistent association between long-term $PM_{2.5}$ exposures and increased mortality that is independent of long-term time trends in $PM_{2.5}$. Our findings are in direct contradiction to conclusions reached by Mr. Holm and Dr. Cox in their comments, reflecting their misreading of Pun et al. (2017) and a lack of consideration of findings from Eum et al. (2018).

cc. CASAC, Jason Sacks, Scott Jenkins

References

[1] Pun VC, Kazemiparkouhi F, Manjourides J, Suh HH. Long-Term $PM_{2.5}$ Exposures and Respiratory, Cancer and Cardiovascular Mortality in American Older Adults. *American Journal of Epidemiology* 2017; 186(8):961-969. PMID: 28541385; doi: 10.1093/aje/kwx166.

[2] Eum K, Suh HH, Pun VC, Manjourides J. Impact of long-term temporal trends in fine particulate matter ($PM_{2.5}$) on associations of annual $PM_{2.5}$ exposure and mortality: An analysis of over 20 million Medicare beneficiaries. *Environmental Epidemiology* 2018; 2(2); e009. doi: 10.1097/EE9.0000000000000009

[3] Greven S, Dominici F, Zeger S, et al. An approach to the estimation of chronic air pollution effects using spatio-temporal information. J Am Stat Assoc 2011; 106(494): 396-406.

[4] Janes H, Dominici F, Zeger SL. Trends in Air Pollution and Mortality: *An Approach to the Assessment of Unmeasured Confounding. Epidemiology 2007;* 18(4), 416-*423.*